

The New Lab Rat Has Gills, Stripes: It's the Zebrafish

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today, Dr. Streisinger, who died during a scuba-diving class in 1984, is considered a visionary.

The National Institutes of Health this fall plans to begin building a \$17.5 million zebrafish facility to house as many as 500,000 of the cold-blooded creatures in 25,000 1 and 2-liter tanks.

Since Dr. Liu added zebrafish to his leukemia research at the National Institutes of Health four years ago, two more researchers have followed suit, and the government institutes hired two new zebrafish researchers, doubling to eight the number of zebrafish labs.

When Alvin Chin, a pediatrics professor at the University of Pennsylvania School of Medicine in Philadelphia, took a sabbatical to do genetics research with zebrafish in 1994, colleagues urged him to go to a mouse lab instead. "They thought I was crazy," says Dr. Chin, who now runs his own zebrafish lab. "Now I don't think anyone disputes that information you find from zebrafish mutation will be relevant to human disease."

While zebrafish can swim circles around mice in some ways, the mouse is superior in others. As mammals, mice are more similar to humans—scientists estimate that humans diverged from mice on the evolutionary ladder 75 million to 80 million years ago—and mice have been studied for about a century. Zebrafish are believed to have diverged from humans as far back as about 450 million years ago, yet researchers have noted a remarkable similarity between human and zebrafish

genes. Often zebrafish and mice are used to complement one another; geneticists may start with zebrafish and move on to mice.

Notably, mouse researchers have developed a way to target a specific gene and knock out only that gene's function. That way they don't have to force mutations in thousands of animals to find the genetic abnormality they want.

That can't be done yet in zebrafish, but the race is on. Researchers at Purdue University, West Lafayette, Ind., last week said they received a \$1 million three-year National Institutes of Health grant to develop a way to target zebrafish genes and turn them off permanently.

But for now, scientists usually add chemicals to force mutations in the zebrafish genes. The researchers then screen the fish and catalog them based on their abnormalities. When a gene is altered, scientists can deduce what traits that gene influences by observing the offspring of the mutant zebrafish.

Some in the pharmaceutical industry believe zebrafish research may lead to the discovery of new drugs. Mark Fishman, a cardiologist who pioneered early genetics studies of zebrafish at Massachusetts General Hospital, last year became global head of research for Novartis AG. The Swiss company's new drug-discovery research headquarters in Cambridge, Mass., now has a zebrafish lab.

The drug maker also is funding research by Randall Peterson, an assistant professor of medicine at Massachusetts General Hospital. Dr. Peterson, who worked with Dr. Fishman before he left for Novartis, puts mutated zebrafish embryos into tiny wells. Then he adds potential drugs and sees if the drugs will reverse the genetic abnormality. "You couldn't screen through thousands of potential drugs in mice," he says. "They're much too big and much too expensive."

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THE WALL STREET JOURNAL

FRIDAY, AUGUST 8, 2003 \$4

Building a Better Lab Mouse— The Zebrafish

By PAMELA CULLEN

IN MEDICAL research labs, mice are the den-

ing of the age of aquarists. Re-
garding aside the trendy laboratory mouse
in certain genetics studies is the zebrafish, a
native of pet stores and home-aquariums. Re-
searchers are using its striped coat to reveal
secrets of diseases of the heart, fat and bone,
as well as leukemia, musculoskeletal and vi-
sual and hearing disorders.

The 1½-inch zebrafish, *Danio rerio*, has been a lab
mouse and reproductive technology for about
2,000 progeny a year, kept and with about 10 off-
spring for a mouse. The zebrafish, which
takes up less space in labs, costs
about \$1 a year to keep, compared with \$80 a
year to maintain a mouse.

Best of all,

unlike a mouse, a
female zebrafish
lays eggs, which
are fertilized out-

side her body. Re-

searchers can

cause the eggs to

develop outside, and

they mature in a



can observe and ma-

nipulate them as they grow.

By contrast, the mouse, which is a mammal,
develops inside its mother's womb. Researchers who
want to see the mouse embryo at a particular stage
of development must kill it and its mother. "You get
only snapshots rather than the whole process," says
P. Paul Liu, a senior investigator at the National
Human Genome Research Institute in Bethesda,
Md. Dr. Liu, a leukemia researcher, added zebrafish
to his mouse lab to study genes that lead to the
formation of blood in embryos.

Another bonus: Zebrafish embryos are
nearly transparent in their early stages of devel-
opment. That means scientists can easily spot
mutations at work as the cells divide and the
embryo develops.

But not everyone applauds the use of the fish
in research. People for the Ethical Treatment of
Animals, which has long fought the use of mon-
keys, mice and other mammals in research, also
opposes the use of zebrafish. "Even though there
is a perception that fish are a so-called lower
species, we don't say that," says Troy Kadle, a
science policy adviser for the organization.

The late George Streisinger, a genetics re-
searcher at the University of Oregon, is widely
credited with developing the zebrafish, native to
the Ganges River in India, as a laboratory ani-
mal. For years, Dr. Streisinger faced skepti-
cism as he pioneered use of the zebrafish (*Danio
rerio*) for genetics studies in the 1970s. Full
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